

Obesity-Prevent rather than cure: Histopathological and clinical Perspectives

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Abstract: Obesity is a modern pandemic. It has turned into a common, serious and costly disorder. Obesity is not just a cosmetic consideration. It is a dire health dilemma directly harmful to one's health. Obesity is a chronic disease affecting increasing numbers of children and adolescents as well as adults. The longer a person is obese, the more significant obesity-related risk factors become. Obesity is increasing in an epidemic manner in most countries and constitutes a public health problem by enhancing the risk for Coronary heart disease, Type 2 diabetes, Cancers (endometrial, breast, and colon), Hypertension, Dyslipidemia, Stroke, Liver and Gallbladder disease, Sleep apnea and respiratory problems, Osteoarthritis, Gynecological problems (abnormal menses, infertility)

INTRODUCTION

The adipocyte number is a major determinant for the fat mass in adults. However, the number of fat cells stays constant in adulthood in lean and obese individuals, even after marked weight loss.

Adipose tissue is a complex, essential, and highly active metabolic and endocrine organ. Adipose tissue not only responds to afferent signals from traditional hormone systems and the central nervous system but also expresses and secretes factors with important endocrine functions. These factors include leptin, other cytokines, adiponectin, complement components, plasminogen activator inhibitor-1, proteins of the renin-angiotensin system, and resistin.

Altered adipocyte function changes production and secretion of adipokines, such as leptin, adiponectin, angiotensinogen, plasminogen activator inhibitor-1, resistin, and several inflammatory molecules.

Fat cells are chemical factories and body fat is potent stuff: a highly active tissue that secretes hormones and other substances with profound and sometimes harmful effects on metabolism, weight and overall health.

DISCUSSION

If a person keeps overeating, fat cells grow rapidly. When they reach the limit, they don't divide; they send out a signal to nearby immature cells to start dividing to produce more fat cells. Thus this starts a cascade of events leading to unlimited proliferation of adipocytes and the more the fat accumulation, more the number of fat cells accumulating fat and more the active division of cells. Thus an exponential growth of fat cells occurs. This can be exemplified by the fact that a typical overweight adult has around 75 billion fat cells. But in the case of severe obesity, this number can be as high as 250 to 300 billion.

Fat cells tend to increase in number most readily when excessive weight is gained due to overeating and or inactivity during the following periods:

- During late childhood and early puberty
- During pregnancy
- Most commonly, during adulthood when extreme amounts of weight are gained

Fat expands in 2 ways

A. Fat Cell Number

- Fat cell number does not decrease with weight loss
- Increases 5 fold until age 22 years
- Increase continues with nutritional excess
- Non-obese person has 25-30 billion fat cells
- Obese person has 260 billion cells

B. Fat Cell Size

- Fat cell size reduces with weight loss

- Adults fill existing fat cells when they over eat

EMBRYOLOGICAL PERSPECTIVE

Infants begin to develop fat cells during the third trimester of pregnancy. Fat cells divide and multiply in the body. When the fat cell is full, it goes through active mitosis, divides in half and becomes two. When both of those two cells become full of fat, they, too, divide. It goes on and on and on. Fat cells do not have the capability of dissolving and leaving the body. Once fat cells develop in the body, they remain there for life. The early rudiments of obesity may hence be laid in early life.

GENETIC PERSPECTIVE: OUR GENES WOULD NOT ALLOW US TO BE NON OBESE

Normally, a gene known as PPAR controls the amount of fat cells that are made and the size of those cells. A mutation in this gene causes switching of the gene to 'on' position causing more fat cells to form and these cells get fatter faster than normal fat cells.

The other gene regulates production of a hormone called "leptin," which suppresses appetite when fat cells become too full. Like PPAR, mutation of this gene occurs in only a small number of people. A subset of obese humans have normal or relatively low leptin levels (H⁷5-10% of subjects)^{1,2}

In well-known animal models such as the ob/ob mouse and the fa/fa Zucker rat, obesity is entirely genetic in origin and is inherited in a classical Mendelian recessive fashion. Exceedingly rare, humans also have obesity attributable to defined mutations in the genes such as those encoding leptin, its receptor and the melanocortin-4 receptor. However, this does not apply to the common type of obesity which is a fine example of a multifactorial disease determined by the interaction between genes and the environment. The very rare human mutations provide important proof of concept that these gene products play a role in normal energy homeostasis, but they do not necessarily tell us much about their role in common human obesity.

Rare but crucial mutations are:

- Leptin Produced by adipose tissue, leptin reduces food intake in rats if centrally injected. Mutation on chromosome 7 found in some obese families
- Leptin receptor CNS receptor for leptin, Mutation on chromosome 1 associated with three cases of human obesity
- Melanocortin 4 receptor involved in the suppression of appetite Mutations on chromosome 18 associated with several cases of obesity
- Prohormone convertase 2 Converts proinsulin to insulin and C-peptide. Polymorphisms on Chromosome 20 are associated with a higher relative risk of NIDDM and obesity

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- Differences in leptin sensitivity and/or leptin production have been suggested to play a role in the pathogenesis of obesity. The majority of human and rodent obesity is associated with hyperleptinemia, suggesting that in these cases leptin resistance is responsible for this condition^{3,4,5}

Microscopic alterations in adipose tissue of obese persons:

Consistently, obesity is associated with Histological changes of the type:

- Increase in numbers of adipocytes,
- Increase in size of adipocytes,
- Infiltration of adipose depots by mononuclear cells
- Relative rarefaction of blood vessels,
- Relative rarefaction of neural structures.

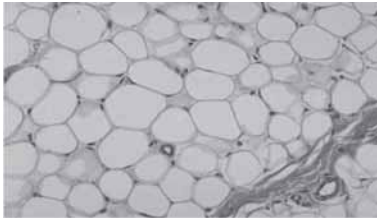


Figure 1: Histological appearance of fat cells. There is a thin cell membrane that bounds the cytoplasmic lipid, which appears clear in this section because normal tissue processing removes lipids. The cell nucleus is pushed to one side by the lipid. Connective tissue septae divide lobules of fat and carry the vascular supply.

Fat cells in obese people are “sick” compared to those in lean people. It has been found that significant differences exist in the fat cells of the obese participants compared with the lean participants.”The fat cells found in obese patients are deficient in several areas.

- The obese people’s fat cells showed stress on the endoplasmic reticulum (ER), which helps cells synthesize proteins and monitor how they are folded. When the ER is stressed, it produces several proteins that ultimately lead to insulin resistance. Insulin resistance, in turn, plays a major role in the development of obesity-related conditions. The differences in the fat cells between obese and lean people may help explain the link between obesity and a higher risk of diabetes, heart disease, and stroke.⁶
- Obese individuals have a relatively large amount of hypertrophic adipocytes compared to lean subjects
- The specific activity of the lipogenic marker enzyme G3PDH was 50% lower in total adipocytes of obese as compared to that of non obese subjects.
- Omental adipocytes from obese subjects also had lower basal lipolytic levels, and a lower lipolytic response to p-adrenergic stimulus. It is possible that the impaired lipolytic response contributes in time to the enlargement of the triglyceride depot. The reduced ability to store additional triglycerides, would result in an increased amount of circulating lipids, elevating the risks associated with the metabolic syndrome.

FAT CELL NUMBERS ARE ‘SET FOR LIFE’

The total number of fat cells per person remained relatively constant over time. Even extreme weight-loss strategies, such as bariatric surgery, do not reduce the number of fat cells No amount of dieting will alter the number of fat-hoarding cells in our bodies

An individual is born with a predetermined number of fat cells, with women generally inheriting more than men. The number of fat cells then grows through late childhood and early puberty, after which it is pretty much set. Fat cell number increases more rapidly in obese children than in lean children. The amount of fat someone has is a reflection of both the number and the

size of the fat cells.

QUANTITY VERSUS SIZE OF FAT CELLS

Fat cell numbers are different between two people yet it is possible for both to have a similar fat percentage. For example if someone had 500 million fat cells and a second person only had 300 million fat cells, these two people could both have a similar fat percentage if the second person has a sedentary lifestyle causing more fat to be stored in his/her cells. That is, the fat cells have become fuller and contain a greater volume within each cell. In this case it would result in a fat percentage higher than normal for this person but around the same as the first person with a higher number of fat cells.

FAT CELLS ONCE GAINED ARE NEVER LOST.

Even if an individual loses weight the size of fat cells is reduced not the number which remains constant. A fat cell is 95% fat. If it dies, it leaves behind insoluble fat, in obese people; the fat tissue often produces too many bad hormones and too few good ones.

It can be safely assumed that once the obesity is set it is difficult if not impossible to reverse the nature of this phenomenon.

THE NUMBER OF FAT CELLS IS GENETICALLY PREDETERMINED

In an individual the number of fat cells present is genetically predetermined as a result of which an individual who has a larger number of fat cells early in life is more prone to get obese as compared to an individual whose is non obese. Accumulation of various characters such as sedentary life style, aggressive eating, too much high calorie diet would complement the genetic trait.

The longer the course of obesity, the more difficult it is to have it treated. The more obese the person more difficult it is to have an effective control.

Two of the Healthy People 2010 national health objectives⁷ are:

- to reduce the prevalence of overweight and obesity among adults to less than 15% and
- to reduce the prevalence of obesity among children and adolescents to less than 5%. This site provides a variety of information designed to help people understand the severity of obesity, the efforts being made to address it, and how to maintain a healthy weight.

RESULT

Given the serious nature of chronic diseases and conditions associated with obesity and the fact that obesity is difficult to treat, prevention is extremely important. The fact that both medical and surgical treatments for curing obesity have not proven to be effective in most cases and the associated adverse effects of these therapies prompts one to realize the need of effective prevention at an early stage with concurrent reduction in the occurrence of other associated diseases.

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